# Misinterpretation of *Stachybotrys* Serology

November 2000

## Background

Recently both scientific inquiry and national news media attention have raised concerns about possible health consequences of human exposure to indoor mold growth. Much of this concern has been generated by discovery of toxigenic mold species in water-damaged buildings. Although not supported by the Centers for Disease Control and Prevention (CDC, 2000), recurring news coverage suggesting a link between the fungus, *Stachybotrys chartarum*, and a series of infant pulmonary hemorrhage cases in Ohio continues to generate public anxiety about possible toxic fungal exposure in homes, schools and workplaces. Toxigenic fungi, including *Stachybotrys*, may or may not produce toxins depending on several factors, including the specific fungal strain and the organic substrate it is metabolizing. Thus isolation of a potentially toxigenic fungus from a building does not indicate that occupants have actually been exposed to mycotoxins. As there are no readily available methods to test building air or materials for mycotoxins, some patients have sought their physicians' help to determine if they have been exposed to toxic indoor fungi.

Local health officers and other health care practitioners have requested assistance from medical personnel at the California Department of Health Services in interpreting the medical and environmental significance of *S. chartarum* serological tests. In some situations serum antibody concentrations to *Stachybotrys chartarum* (previously known as *S. atra*) have been misinterpreted, leading to erroneous diagnoses, unwarranted biomonitoring and environmental testing, and arousing needless patient and community apprehension. The following information is provided to update health care providers regarding the use of this test method.

## Is there a *Stachybotrys* biomarker?

A urine or serum toxin-specific biomarker (as is available for aflatoxin, the carcinogenic metabolite of *Aspergillus flavus*) would be the ideal method to determine exposure to toxins produced by an indoor fungus. However, at this time there are no valid biomarkers for the toxins potentially produced by *Stachybotrys chartarum.* Some physicians have used serum antibodies to *Stachybotrys* antigens as an indicator of exposure (to the fungus or its toxins) and/or disease. *Stachybotrys* serology is commercially available from only one laboratory in the U.S. IBT Reference Laboratory in Lenexa, Kansas has developed an isotype-specific ELISA method to measure *S. chartarum* IgE, IgG and IgA. IBT has also determined the performance characteristics of these procedures. FDA has not evaluated or approved these testing methods.

Like any other testing procedure used in clinical medicine, the validity of *Stachybotrys* serology should be evaluated by determining its sensitivity, specificity, and especially its positive and negative predictive values prior to its widespread use. Research studies to provide this information have not yet been carried out. At this time more carefully conducted studies are needed to determine the utility of *Stachybotrys* serology for diagnosis of clinical disease or as an indicator of *Stachybotrys* environmental exposure.

## Fungal allergens – more problematic than pollen and other common antigens

Development of fungal serological methods has been hampered by difficulty in producing and working with fungal allergen extracts (Burge 1985, Horner et al. 1999). An individual fungal species is typically capable of producing many allergens. These allergens are variably produced depending on the fungal strain cultured, laboratory conditions, fungal growth stage and substrate being metabolized (Helm et al. 1987). Studies have shown considerable cross-reactivity among allergens of related fungal species and even genera (DeZubiria et al. 1990).

## Stachybotrys-specific serology – clinical diagnostic value

In general, antigen-specific IgA occurrence is not clinically relevant to diagnosis of allergic disease or hypersensitivity disorders, although it does have some utility in the work-up of certain systemic infections (Kishiyama 1999). Elevated IgE or IgG levels to well characterized fungal antigens (such as Alt a 1 from *Alternaria alternata* or Asp f 1 from *Aspergillus fumigatus*) along with appropriate history, physical exam findings and other diagnostic procedures can assist in diagnosing fungal allergy or hypersensitivity pneumonitis respectively. However, clinicians must recognize that most currently available commercial fungal immunological procedures have questionable specificity due to lack of purified or standardized fungal allergen extracts.

The IBT *S. chartarum* antigen was recently shown to cross-react with antibodies to *Aspergillus fumigatus* and *Alternaria alternata*, two common outdoor fungi (Halsey 2000). Thus a positive *S. chartarum* test result does not necessarily mean the patient has developed antibodies to *Stachybotrys*. Rather, the patient may have been exposed to an entirely different fungus that shares certain immunologic characteristics with *S. chartarum*.

In addition, studies evaluating the prevalence and concentration of *S. chartarum* antibodies in the general population have not been conducted. The IBT reference range for *S. chartarum* serologic tests was estimated by measuring the antibody responses of 41 adults with no known fungal-related disease. The upper threshold was set at 2 standard deviations above the mean. Therefore the true range of antibody concentrations in the general public with no exposure to moldy buildings is not known.

## Correlation of antibody prevalence with environmental *S. chartarum* exposure

Some clinicians have interpreted the presence of *S. chartarum*-specific IgA or IgG antibodies as evidence of recent or chronic exposure, respectively, to this fungus. Generally, IgA antibodies are relatively short-lived. However, the kinetics of IgA synthesis and breakdown show large inter-individual variability and also depend on exposure to related or cross-reacting antigens from other fungi (Halsey 2000). IBT Laboratory has also indicated that kinetics of decline for IgG antibodies are not predictable and cannot be used to establish the date of last exposure to *Stachybotrys chartarum* or other fungal cross-reacting antigens. The demonstrated cross-reactivity of the *S. chartarum* antigen indicates that antibody response to this antigen cannot be used to prove exposure to this fungus.

## *Stachybotrys* serology – case study experience

Several case-control studies have utilized serology in office building investigations with documented presence of large amounts of *Stachybotrys*. These investigations found no statistically significant differences in *Stachybotrys*-specific IgG or IgE concentrations between exposed and control groups (Johanning 1996, 1999; Hodgson 1998). A recent case-control study of water-damaged or mold-contaminated homes in Finland found fungal-specific IgG concentrations in both cases

and controls, with cases showing a tendency for higher antibody levels than the control group to most fungi (Hyvärinen 1999). However the fungal species identified in the case homes frequently did not correlate with the most prominent fungal antibodies in case patients. Researchers have also found high levels of *Stachybotrys*-specific IgG in some members of their control groups who had no evident exposure to this fungus in the home or workplace under investigation (Johanning 1996, Hyvärinen 1999).

## Summary

The demonstration of mold-specific antibodies alone is generally considered insufficient to prove that health effects reported by individuals in moisture-damaged buildings are caused by mold exposure. Symptoms associated with mold exposure are nonspecific and vary greatly with individual susceptibility. There are currently no validated biomarkers of exposure to specific indoor fungi or their toxins. *Stachybotrys chartarum* serology tests have no clinical application at this time. They cannot be used to imply the presence of Stachybotrys within a home or workplace environment, nor can they be used to prove patient exposure to this specific mold or its toxins.

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